PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: CYTOGEN Corporation

For: U.S. Patent No. 5,162,504

Issued: November 10, 1992

Inventor: Julius S. Horoszewicz

Title: MONOCLONAL ANTIBODIES TO A NEW ANTIGENIC MARKER IN EPITHELIAL PROSTATIC CELLS AND SERUM OF PROSTATIC CANCER PATIENTS

April 11, 1997

HAND DELIVERY

Petitions Office
Special Programs
Crystal Plaza 1
Suite 520

ATTN: KARIN TYSON

In accordance with your instructions during our telephone conference on April 7, 1997, I am having hand delivered duplicates of a supplement to an Application for Extension of Patent Term Under 35 U.S.C. 156.

Thank you for your assistance.

Wendy L. Davis
Reg. No. 38,427
Agent for Applicant

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: CYTOGEN Corporation	] Legal Advisor: Karin Tyson
	]
U. S. Patent No.: 5,162,504	] Re: Application for Patent
	] Term Extension
Issued: November 10, 1992	]
	]
	] April 11, 1997

Commissioner of Patents and Trademarks
Box 10, Patent Extension
Washington, D.C. 20231

Dear Sir:

In a telephone call to W. Scott McNees of Cytogen Corporation, on February 26, 1997, from Karin Tyson, Legal Advisor, Special Program Law Office, Ms Tyson noted that the above-noted application fails to satisfy the requirements of 37 CFR 1.740(a)(11). This section calls for a brief description of significant activities undertaken by the Applicant during the applicable regulatory review period and the corresponding dates of such activity. Responsive to the above-noted conversation and in accordance with 37 CFR 1.740(a)(11), Applicants submits the following:

A brief description of the significant activities undertaken by the Applicant during the applicable regulatory review period with respect to the Product (as defined in the above-noted application) and the significant dates applicable to such activities are as follows:

a) During the testing or IND period, the significant dates and activities were as follows:

Index BB-IND 3311
Indium In 111 CYT-356

Serial No. 000 9/26/89	Orginal submission (accession No. 102785)
10/14/89	**Issuance of IND number**
Serial No. 001 11/6/89	Responses to FDA's comments and questions
Serial No. 002 1/9/90	Protocol Amendment: New Investigators, B. David Collier M.D., (Medical College of Wisconsin); Gary Winzelberg, M.D., (Shadyside Hospital); Charles Neal, M.D., and J. G. Katterhagen, M.D., (Medical Center); Information Amendment: Termination of Temple; process change for preparation of CYT-356; test results for lots Y9J0140 and Y9J0138; changes in IND Section 7 (bacterial endotoxin and sterility for NaOAc; sterility for bulk; mycoplasma)
Serial No. 003 3/7/90	Protocol Amendment: New Investigators, Hani Abdel-Nabi M.D., Ph.D., (VA Medical Center); Edith P. Mitchell, M.D., (University of Missouri); Gary L. Purnell, M.D., (McClellan VA Hospital)
Serial No. 004 4/19/90	Protocol Amendment: New Investigators, Samuel Halpern, M.D., (VAMC SD); Ian Tyson, M.D., and Albert V. Heal, Ph.D., (James A. Haley VA Tampa) Information Amendment: Evaluation of 0.1 mg dose at SIU.
Serial No. 005 6/1/90	Information Amendment: Test results for lots Y0K0170 and Y0K0171; Report on first segment of clinical study; Addition of MRI and CT tests as confirmatory measurements; additional subinvestigator at McClellan VA Hospital for Medical Sciences.
Serial No. 006	Information Amendment: Discussion regarding clinical

6/13/90	protocol (FDA confirmation of beginning enrollment of group 1 pts).
Serial No. 007	Protocol Amendment: New Investigators, Harwood,
Hudson,	
11/6/90	Bay Pines; Serafini, Jackson Memorial Termination Shadyside, University of Missouri.

Serial No. 008 12/19/90	1st Annual Report, Revised Investigator's Brochure Protocol Amendment: New Investigators 356In10 (Daniel Kahn, M.D., George Weiner, M.D., University of Iowa Hospitals and Clinics). Information Amendment: DMF update Amersham 5472, protein concentration added; Termination VAMC San Diego
Serial No. 009 1/31/91	Information Amendment: Test results for CYT-356 Lot Y0S0258A (10mg/2mL)
Serial No. 010 3/13/91	Protocol Amendment: New Protocol 356In11, Amendment 1 to Protocol 356In11 Information Amendment: Termination of University of Arkansas.
Serial No. 011 6/11/91	Information Amendment: Test results for CYT-356 Lot Y1M0317A, Termination of Medical College of Wisconsin, Memorial Medical Center, Buffalo VA Medical Center, James A. Haly VA Tampa, Bay Pines VA Medical Center, Jackson Memorial Hospital, University of Iowa Hospitals and Clinics.
Serial No. 012 6/26/91	Protocol Amendment to 356In11 (Amendment 2): Change in dose to 0.5 mg, starting with 6-7 mCi of indium-111, adding all NaOAc.
Serial No. 013 07/08/91	Protocol Amendment: New Protocol 356In12, (Michael Haseman, M.D., Sutter General Hospital).
Serial No. 014 07/29/91	Protocol Amendment: New Investigator, Protocol 356In11 (Medical College of Wisconsin); New Investigators, Protocol 356In12, (SIU, SUNY Buffalo, Jackson Memorial, UC Davis). Information Amendment: Amendment 1 to Protocol 356In12

Serial No. 015 07/30/91	Information to request meeting for clinical discussion.
Serial No. 016 09/11/91	Protocol Amendment: New Investigators, Protocol 356In11, (Albert Heal, M.D., Ian Tyson, M.D., James A. Haley, V.A.); Steven Harwood, M.D., Bay Pines); Protocol 356In12, (Henry Goodgold, M.D., St. Louis University, George Weiner, M.D., University of Iowa); Deletion of subinvestigator at 356In12 (Frederick Myers, U.C. Davis Medical Center)
Serial No. 017 11/7/91	Protocol Amendment: New Investigators, Protocol 356In12, (Brian McCandless, M.D., Albany; Alan Keller, M.D., St. Francis Hospital; Ian Tyson, M.D., Albert Heal, Ph.D., University of South Florida; David Collier, M.D., Medical College of Wisconsin; Joseph Babaian, M.D., M.D. Anderson). Information Amendment: Cross reference letter, Nordion International, Inc. DMF-8985
Serial No. 018 (12/4/91	Protocol Amendment: New Investigator, Protocol 356In11 (George Weiner, M.D., Daniel Kahn, M.D.); Additional subinvestigator at Protocol 356In12 (Srikic Chandallpaty, M.D., at Jackson Memorial Hospital) Information Amendment: Amendment 2 to Protocol 356In12, (New, Patient Management Criteria which must be utilized in joint review of each case by urologist and nuclear medicine physician, Phase 2 goals - patient enrollment - 40 pts)
Serial No. 019 12/17/91	Protocol Amendment: New Investigator, Protocol 356In12 (Paul F. Schellhamner, M.D., Eastern Virginia Medical School)
Serial No. 020 01/28/92	Annual Report, Revised Investigator's Brochure Protocol Amendment: New Investigators, Protocol 356In12 (Gerald Chodak, M.D., Univ. of Chicago; Richard Ostenson,

M.D., Good Samaritan Hospital; Paul Lange, M.D., University of Washington School of Medicine-Seattle; Michael J. Manyak, M.D., George Washington University Medical Center), New Protocol 356In14 (George Weiner, M.D., Daniel Kahn, University of Iowa Hospitals and Clinics)

Serial No. 021
02/18/92

Protocol Amendment: New Investigators, Protocol 356In12 (William R. Morgan, M.D., Yale University School of Medicine-New Haven, CT; John Lynch, M.D., Georgetown Univ., Med School-Washington, DC), Change in Protocol 356In12 (clarify inclusion criteria-specific PSA kit by manuf. name)

Serial No. 022 03/26/92	Protocol Amendment: New Investigator, Protocol 356In14 (Charles Neal, M.D., Memorial Med. Cntr, Springfield, IL) Information Amendment: Change in Protocol 356In12; use of referring hospitals at Univ. of S. Florida. Additional information on patient #356In14-193-001
Serial No. 023 04/02/92	Information Amendment: Review of phase 2 clinical results: Proposal for initiating pivotal clinical trials: protocol 356In15
Serial No. 024 (05/07/92	Protocol Amendment: change in Protocol 356In14; 2nd group of patients, enrollment = 40, 8 week physical exam, follow-up forms every 6 mos., follow-up physical at 1 week, data between groups 1 & 2 analyzed separately. Information Amendment: Revised Form 1572 for Charles Neal; new investigator Protocol 356In15 (A. Sardi, M.D., and S. Bardot, M.D., Ochsner Medical Cntr, New Orleans, LA)
Serial No. 025 06/19/92	Protocol Amendment: New Investigator, Protocol 356In14 (Hani Nabi, M.D., SUNY), New Investigators, Protocol 356In15 (Allan Keller, M.D., St. Francis Hospital, Tulsa, OK; Charles Neal, M.D., Memorial Med Center, Springfield, IL) Information Amendment: Changes in IND Section 7 (manufacture and purification of CYT-351 in-house), (bulk release specifications, final container release specifications), lot results for Y2M0581
Serial No. 026 07/08/92	Protocol Amendment: New Investigators, Protocol 356In14 (A. Sardi, M.D. & S. Bardot, M.D., Alton Ochsner Research Center, New Orleans, LA), New Investigator, Protocol 356In15 (P. Schellhammer, M.D., Sentara Norfolk Gen. Hosp., Norfolk, VA) Information Amendment: Clinical - Amendment 5 to Protocol 356In12 & Amendment 1 to Protocol 356In15 (radiation dosimetry evaluations), Termination of Protocol

356In12 at 5 clinical sites

Serial No. 027 09/10/92	Protocol Amendment: New Investigators, Protocol 356In14 (PH Lange, Univ. Washington Med Cntr & Seattle VA Med Cntr, Seattle, WA); Protocol 356In15 (B. McCandless, Albany Med Cntr, NY; AB Brill, Univ. Mass. Med Cntr, Worcester, MA; TR Hakala, Presbyterian Univ. Hosp., Pitts, PA; JE Montie & L. Davis, Wayne State Univ., Detroit, MI; R. Weissman, Virginia Mason Med Cntr, Seattle, WA; MJ Manyak, Geo. Washington Med Cntr, Wash, DC; D. Kahn & G. Weiner, VA Med Cntr, Iowa City, IA; HA Nabi, SUNY, Buffalo, NY); Change in Protocol 356In11 (Amendment 3)
Serial No. 028 10/09/92	Protocol Amendment: New Investigators, Protocol 356In15 (Paul Lange, M.D., U of Washington Med Cntr, Seattle, WA; R. Joseph Babaian, M.D., M.D. Anderson, Houston, TX); Change in Protocol 356In14, Amendment 2 (radiation dosimetry and pk evaluations) Information Amendment: Protocol 356In14, Amendment 3 (additional SPECT imaging session); Protocol 356In15, Amendment 2 (standardized surgical procedures); Tests results for Y2T0468A
Serial No. 029 10/23/92	Information Amendment: Clinical, Change in Protocols 356In11, 356In14, 356In15 (camera quality); New investigators, protocol 356In14 (J.L. Mohler, M.D., Univ of North Carolina, Chapel Hill; D. Petrylak M.D. & C. Olsson, M.D., Columbia Presbyterian Med. Cntr. NY); Termination of Protocol 356In12; Test Results for 356 Lot Y2T0468A
Serial No. 030 11/18/92	Responses to July 6, 1992 telephone conference (serum-free cell banking; comparison of CYTOGEN/Invitron CYT-351; DMF-8474, 8475; "end of production cells"; testing of harvests; viral clearance data for CYT-351; release tests for pre-purified product; IEF testing of bulk/final product)

Serial No. 031 (12/4/92	**New Investigators, Protocol 356In14** (Perinchery Narayan, M.D., Vet Admin. Med Cntr and Univ. of CA at San Francisco, Leonard Freeman, M.D., Montefiore Med Cntr, Bronx, NY; David Seldin, M.D., Lahey Clinic Med Cntr, Bulington, MA), **Protocol 356In15** (Leonard Freeman, M.D.; David Seldin, M.D.; Perinchery Narayan, M.D. [see above for sites], John Olsen, M.D., Ohio State Univ. Med. Cntr, Columbus, OH; Alan Waxman, M.D., Cedar Sinai, LA, CA) **Subinvestigator, Protocol 356In15** (J. Crist Reynolds, M.D., St. Francis Hosp., Tulsa, OK), **Change in Protocols 356In11** (number of repeat doses no longer restricted, Amendment 5), **and Protocol 356In14** (Group III patients who have undergone radiotherapy, Amendment 5), **Termination of 356In11 at one site** (Medical College of Wisconsin), **Test Results for CYT-356** (lot Y2A0460DA)
Serial No. 032: 1/20/93	1992 Annual Report, Revised Investigator's Brochure
Serial No. 033: 2/3/93	Protocol Amendment: New Investigators 356In14 (Gerald Chodak, Univ. of Chicago Hosp; Michael Manyak, Geo. Washington Univ., Washington DC) 356In15 (Gerald Chodak, Richard Brown, Crittenton Hosp, Rochester, MI)
Serial No. 034: 2/22/93	Compassionate use in Protocol 356In14 (Dr. Bardot, Oschner Clinic)
Serial No. 035: 3/8/93	Protocol Amendment: New Investigator, Protocol 356In14 (J. Babaian, Univ. of Texas MD Anderson) and 356In15 (J. Lynch, Georgetown Univ. Wash DC) Information Amendment: Revised 1572 (Cancer Care Assoc. change of address); Termination of Protocol 356In11 at 2 clinical sites (James A. Haley Hosp, Bay Pines VA Med Cntr)
Serial No. 036:	Serial no. skipped to be consistent with FDA numbering.
Serial No. 037: 5/13/93	Protocol Amendment: Change in Protocol 356In14 (repeat infusions of indium In 111 CYT-356); Additional

	Subinvestigator, Protocol 356In15 (Pat J. Loianono, M.D., Sentara Norfolk Gen Hosp.)
	Information Amendment: Revised 1572, Protocol 356In15 (T. Hakala, M.D., Univ. Pittsburgh office location - no more clinical inv. at Veteran's Administration Med Cntr.)
Serial No. 038: 7/8/93	Protocol Amendment: New Investigator, Protocol 356In14 (John Lynch, M.D., Georgetwon Univ. Hosp.) and 356In15 (Robert Carretta, M.D., Roseville Commun. Hosp.)
	Information Amendment: Termination of Protocol 356In15 at 3 clinical sites (Albany Med Cntr, Cedars Sinai Med Cntr, Virginia Mason Med Cntr.)
Serial No. 039: 9/10/93	Protocol Amendment: New Protocol 356In17 (Daniel Kahn, M.D., Univ. Iowa Hosp. & Clinics); New Investigators, Protocol 356In15 (Gerald Kirk, M.D., Loma Linda Univ.; Harold Atkins, M.D., State Univ. of New York at Stony Brook; Frederick Datz, M.D., Univ. of Utah Med Cntr); Additional Subinvestigators, Protocol 356In15 (Michael Marks, Geo. Wash. Univ. Med Cntr; Glen Gerber, Weiss Mem. Hosp)
	Information Amendment: Termination of Protocol 356In14 at 1 Clinical Site (SUNY at Buffalo); Termination of Protocol 356In15 at 3 clinical sites (Critterton Hosp., Wayne State Univ., St. Francis Hosp.)
Serial No. 040: 11/2/93	End-of-Phase-2 Report (Protocol 356In16); Commercial manufacturing plan and phase 3 clinical development plan (CYTOGEN serum-free process (C); RR-1103, TPs)
Serial No. 041: 11/15/93	Protocol Amendment: Additional Subinvestigator, Protocol 356In14 (Michael Marks, MD, Geo Washington Univ. Med Cntr); New Investigator, Protocol 356In15 (David McLeod, MD, Walter Reed Army Med Cntr, Washington, DC)
	Information Amendment: Termination of Protocol 356In15

	(Loma Linda Univ. Med Cntr, Roseville Community Hospital, Presbyterian Univ. Hosp, Sentara Norfolk Gen. Hosp.)
Serial No. 042: 12/10/93	Protocol Amendment: New Protocol 356In16 (Daniel Kahn, Univ of Iowa Hosp & Clinics, & Iowa City VAMC), Amendment 1 to Protocol 356In16
Serial No. 043: 1/19/94	General Correspondence: Compassionate Use in Protocol 356In14 ((D. Petrylak, Columbia-Presbyterian Med Cntr, NY)
Serial No. 044: 1/24/94	1993 Annual Report, Revised Investigator's Brochure
Serial No. 045: 1/27/94	Correction to Serial No. 040 (corrected version of Attachment 1)
	Protocol Amendment: New Investigators, Protocol 356In16 (M. Manyak, George Washington Univ. Med Cntr; M. Haseman, Sutter General Hospital; D. Seldin, Lahey Clinic)
Serial No. 046: 3/23/94	Protocol Amendment: Change in Protocol 356In11; Change in Protocol 356In14; Protocol 356In15, New Investigators: A. Frankel, Medical University of South Carolina; Protocol 356In16, New Investigators: F. Datz, U of UT,; P. Narayan, UCSF;A. Frankel, Medical University of South Carolina; R.J. Babaian, MD Anderson Cancer Center (1572's and CV's sent for all)
Serial No. 047: 4/4/94	New Protocol 356In19, Change in Protocol 356In19, Test Results for CYT-356 (Lot Y4D0843), David Seldin, Lahey Clinic submitted as investigator on 356In19, Change in IND Section 7, Revised labeling Specifications, Information Amendment: Cross Reference letter, Hyclone Laboratories, Inc.
Serial No. 048: 4/11/94	Protocol Amendment: Change in Protocol 356In11, New Investigator (J. Olsen, Ohio State University Medical Center), Protocol 356In11; Change in Protocol 356In16,

	New Investigators (D.G. McLeod, Georgetown University; J. Olsen, Ohio State University Medical Center), Protocol 356In16; Change in Protocol 356In19, New Investigator (M. Haseman, Sutter General Hospital)
Serial No. 049: 5/10/94	Information Amendment: Revised Form FDA 1527 (add Sireci as subinvestigator); Protocol 356In14; New Investigators, Protocols 356In15 (A. Passalaqua - Summa Health System/Akron City Hospital, Akron Ohio; M. Blute - Mayo Clinic, Rochester, MN), 356In16 (M. Blute, A. Passalaqua, D. Petrylak - Columbia Presbyterian Medical Center, NY, NY), and 356In19 (A. Frankel, Medical University of South Carolina [MUSC], Charleston, SC)
Serial No. 050: 5/26/94	Response to FDA request for information: CBER's questions concerning recloning of CYT-351 cells before preparation of new serum free cell banks.
6/17/94	**Questions on 11/2/93 submission**
Serial No. 051: 6/29/94	Protocol Amendment: 356In14 & 15 Amendments 2A & 1A (radiation dosimetry evaluations); New Investigator, **Protocol 356In11** (D. Seldin - Lahey Clinic, Burlington, MA); **Protocol 356In14**: Revised Form FDA 1572 (D. Seldin, Lahey Clinic, Burlington, MA and P. Narayan VAMC, San Fran, CA); **Protocol 356In15**: New Investigator (H. Clarke, Emory University, Atlanta, GA) and Revised FDA Forms (D. Seldin, Lahey Clinica, Burlington, MA and P. Narayan, VAMC, San Fran, CA); **Protocol 356In16**: New Investigators (P. Lange, U Wash, Seattle, WA, J. Mohler, UNC, Chapel Hill, NC and H. Clarke, Emory University, Atlanta, GA)
Serial No. 052: 7/21/94	New Method for End User Indium 111-labeling of capromab pendetide. Decrease in the amount of sodium acetate used in preparation of the final product.

Serial No. 053: 8/4/94	Protocol Amendment: New Investigators **Protocol 356IN16** (L. Freeman - Montefiore Medical Center, Bronx, NY; D. Sodee - MetroHealth Medical Center, Cleveland, Ohio); **Protocol 356IN19** (R. Babian - MD Anderson Cancer Center, Houston, TX) Also a revised 1572 form for D. Seldin.
Serial No. 054: 8/24/94	Meeting Request. Pre-meeting package of information (proposed PLA TOC, Outline of Clinical Summary, Sample CRR and Data Listings, Draft Package Insert).
Serial No. 055: 8/26/94	Response to FDA request for information - CMC issues.
Serial No. 056: 8/30/94	Response to FDA request for information - Dr. Mills Treatment algorithms charts, overheads, and references cited. Submitted to the IND at the request of Dr. George Mills.
Serial No. 057: 9/1/94	Protocol Amendment: New Protocol, New Investigators **Protocol 356In20** submitted with Amendments 1 and 1A. Investigator: Manyak. **Protocol 356In11** new investigator Haseman; **Protocol 356In19** new investigators Daniel Kahn and Paul Lange. New lab facility for Dr. Babaian. Amendment 1B for **Protocol 356In15**.
Serial No. 058: 9/21/94	REQUEST FOR PRE-PLA MEETING
10/5/94	**Questions on 5/27/94 submission**
Serial No. 059: 10/10/94	Protocol Amendment: New Investigators **356In11**: Lange, Brill. **356In16:** Basler, Waxman, Presti (replaced Narayan). **356In19:** Petrylak. **356In20:** Brill.
Serial No. 060: 10/25/94	Conference Call Minutes; Response to Chemistry Issues. Minutes of 10/18 conference call (discussion of clonality and other manufacturing issues). Submission of a protocol for a clonal verification study and responses to issues

	regarding viral removal/inactivation and the immunoreactivity assay.
Serial No. 061: 10/25/94	Information Amendment: Publication Information provided to George Mills per his request.
Serial No. 062: 11/14/94	PRE-PLA MEETING DOSSIER (hand-delivered to FDA on 11/15/94)
11/15/94	**Questions on 8/30/94 submission**
Serial No. 063: 11/18/94	Information Amendment: Clinical Submission of image data on magnetic discs and selected prints.
Serial No. 064: 11/21/94	Protocol Amendment: New Investigators **356In19:** Freeman. **356In20:** Seldin, Neal.
12/22/94	**Reply to 10/25/94 submission**
Serial No. 065: 1/12/95	Response to FDA letters dated 10/5, 11/15, and 12/22/94. Issues: Clonality post-conversion to serum free media, Viral removal, immunoreactivity assay (Lindmo), and affinity assay (fluorescence quenching).
Serial No. 066: 2/8/95	Prot. Amend.: New Investigators, **Pre-PLA Meeting Minutes** **356In20:** John Olsen (Ohio State U.), Frederick Datz (Univ. of Utah).
Serial No. 067: 3/8/95	Protocol amendment: New Investigator, 356In11 - Michael Manyak, George Washington University Med Ctr; New Investigators, 356In19 - D. Bruce Sodee, MetroHealth Med Ctr; Michael Blute, Mayo Clinic
4/6/95	**Request for progress report**
Serial No. 068: 5/1/95	Annual Report; Change in contact person (add L. Suttner)
Serial No. 069:	Protocol amendment: New Protocol - informed third party

5/3/95	evaluation, May 12-14, 1995.
Serial No. 070: 3/26/95	Clinical information amendment
Serial No. 071: 6/27/95	Protocol Amendment: New Protocol, New Investigator, **356In21**, Michael Haseman, Sutter General Hospital; 356In11 - Amendment 8.
Serial No. 072: 8/29/95	Protocol Amendment: 356In21: New Investigators - Leonard Freeman, Montefiore Medical Center; Daniel Kahn, Iowa VAMC; Samuel Kipper, Tri-City Medical Center; Robert J. McDonald, Providence St. Vincent Medical Center; Hani Nabi, SUNY at Buffalo; Richard Rome, John Peter Smith Hospital; D. Bruce Sodee, MetroHealth Medical Center
Serial No. 073: 9/29/95	Protocol Amendment - New Investigators: 356In21 Charles Neal, Memorial Medical Center; Eric Klein, Cleveland Clinic Foundation; William Carpentier, Scott & White Memorial; David Collier, Section of Nuclear Medicine; Oliver Sartor, Louisiana State University medical Center; James Sylvester, Our Lady of Lake Regional Medical Center; Richard Meidinger, St. Francis Hospital and Medical Center; Hadyn Williams, Georgia Baptist Medical Center
Serial No. 074: 10/31/95	Protocol Amendment - Protocol **356In21**, Amendment 1 Protocol Amendment - New Investigators: 356In21 Paul Sirotta, Lehigh Valley Hospital; Michael Blend, University of Illinois Hospital; Albert Brady, Harris Methodist Oncology Program; Lawrence Davis, Harper Hospital; Marc Coel, Queens Medical Center; Joseph Basler, Jewish Hospital;
Serial No. 075 11/20/95	Study 356In16 Analysis Plan
Serial No. 076 12/4/95	Protocol Amendment - Protocol 356In21 - New Investigators: Michael Manyak, George Washington University Medical Center; Michael Blute, Mayo Clinic; John Olsen, Ohio State University Hospital

Serial No. 077 12/7/95	Study 356In16 Analysis Plan
1/5/96	Export request for Clinical Investigations
Serial No. 078 1/10/96	New Investigators: 356In21: Michael McBiles, Brooke Army Medical Center; Barry Gubin, Research Medical Center
Serial No. 079 2/14/96	New Investigators: 356In21: Kastytis Karvelis, Henry Ford Hospital; Alan Waxman, Cedars-Sinai
Serial No. 080 3/12/96	New Investigators: 356In21: Paul Lange, University of Washington; John Petronis, John Hopkins; A. Michael Kistler, St. Lukes Medical Center; Richard Babaian, MD Anderson; Test Results for CYT-356
Serial No. 081 4/12/96	New Investigators: 356In21: Josef Machac, Mount Sinai Medical Center; Daniel Petrylak, Columbia Presbyterian Medical Center
Serial No. 082 4/23/96	Annual Report: September 27, 1994 to September 26, 1995; Preclinical research reports as information amendment: RR 1201.01/ RR 1231
Serial No. 083 5/15/96	Protocol Amendment: New Investigators; Protocol 356In21; Mary Hart, Morton Plant Hospital; M J Guiberteau, St. Joseph's Hospital
Serial No. 084 6/14/96	Protocol Amendment: New Investigators; Protocol 356In21; Aldo Serafini, University if Miami
Serial No. 085 7/26/96	Protocol Amendment: 356In21: New Investigator: Otis Ball, Mississippi Baptist Hospital
Serial No. 086 8/19/96	Protocol Amendment: 356In21: New Investigators: Judith Joyce, Western Pennsylvania Hospital; Jon Kotler, Holy Cross Hospital; Paul Schellhammer, Sentra Cancer Center; Robert McIntire, Nebraska Methodist Hospital

SN 087 9/16/96	Protocol Amendment: 356In21: New Investigators: John Libertino, Lahey Clinic Medical Center; R. Michael Fleming, Methodist Central Hospital; James L. Mohler, University of NC at Chapel Hill; Robert Schor, Swedish Hospital and Medical Center; Leonard Marks, Suite 701 Medical Plaza
10/16/96 SN 088	Protocol 356In21: New Investigator: Frederick Weiland, Sutter Roseville Medical Center
11/18/96 SN 089	Protocol 356In21: New Investigators: Letty Lutzker, St. Barnabas Medical Center; William Klingensmith, Porter Care Hospital; Calvin Lutrin, Good Samaritan Regional Medical Center; Italo Zanzi, North Shore University Hospital
2/18/97 SN 090	Annual Report - 9/27/95 through 9/26/96

b) During the review or PLA period, the significant dates and activities were as follows:

95-0041
Capromab Pendetide (CYT-356)
Product License Application

Date	Jacket	Description
1/12/95		Submission of PLA and ELA
1/12/95		Submission of $104,000 for User Fee to cover PLA/ELA for ProstaScint
1/17/95		**Receipt of cheque for NDA 1164DM0412JAN95**
1/19/95		**Issuance of reference number for PLA application**
1/18/95		**Request for SAS diskettes**
1/25/95		Submission of Imaging Diskettes (SAS)
2/3/95		Debarment Certification
2/7/95		Submission of SAS datasets
2/7/95		Additional copies of individual volumes
3/3/95		Draft Demonstration Disc and Information for ProstaScint PLA Clinical Data Analysis
3/7/95		Responses to FDA Requests for Information, Conference Call Minutes and Publications
3/13/95		**Confirmation of application being filed**
3/14/95		Indium NDA Cross-Reference Letter
3/15/95		Coming soon poster
3/27/95		Letter to Leon Epps
3/31/95		Coming soon poster for SNM/AUA conventions
4/13/95		Responses to FDA Requests for Imaging Session Data
4/20/95		SAS Datasets
4/28/95		Response to FDA Request for Information - 356In12, 356In15
5/9/95		Response to request for information - 356In12, 356In15
5/10/95		Invitation for symposium at the SNM convention

6/1/95	Revision to Proposed Indication
6/2/95	2x2 table for Informed Third Party evaluation
7/6/95	Meeting schedule for Dr. Zoon/Michael Beatrice
7/12/95	**Not approvable letter**
7/14/95	Follow up to meeting w/ FDA and Not-Approvable letter
7/17/95	Notification of intention to submit an amendment in response to Not-Approvable letter
8/8/95	Response to telephone request for information from Dr. Mills
8/8/95	Pre-Meeting Dossier
8/15/95	Request for 2nd half of User Fee Payment for PLA
8/18/95	Meeting w/ FDA re issues defined in Not-Approvable letter
8/30/95	Payment of 2nd half of User Fee $104,000
10/13/95	Notification of "Consensus conference"
10/23/95	Request for clarification of description of ProstaScint from letter of 7/12/95
11/8/95	Preliminary response to Not-Approvable letter
11/16/95	Change in Responsible Head
1/24/96	Amendment to PLA in response to Not-Approvable letter
1/25/96	Response to Not-Approvable letter and Amendment to the Application
1/29/96	SAS Datasets omitted from 1/25/96 package
1/29/96	Study 356In16 images on optical discs
2/2/96	Additional Copies of 1/25/96 submission
3/4/96	Brochure to announce contract manufacturing capabilities
3/18/96	Request for meeting to facilitate PLA review process
4/8/96	Additional information requested by Dr. Mills on 2/29/96
5/7/96	Confirmation of FDA requests from conference call of 5/2/96

5/14/96	Response to request for information
5/23/96	Radiation dosimetry reports to Michael Stabin at ORISE, TN
5/23/96	Copy of letter to Stabin to FDA
5/24/96	**Questions from Dr. George Mills re cases.**
5/28/96	**Request from Dr. Mills re history of changes to imaging techniques**
5/29/96	**Questions from Dr. Mills re proposed indication**
5/30/96	**Comments from Dr. Mills re Technical Manual**
5/30/96	**Discussion with Dr. Mills re recurrent disease indication**
6/7/96	Response to FDA questions from May 2 conference call.
6/4/96	**Discussion with Mr. Freas re: demonstration of images prior to open session of Advisory Committee**
6/7/96	**Request by Dr. Mills for numerators and demonimators**
6/10/96	Prosposed agenda for 6/18/96 meeting
6/11/96	**Letter from FDA re their letter of July 12, 1995, and our responses of 1/25/96, 1/29/96, 2/2/96, 5/14/96 re efficacy**
6/11/96	**Conference call at request of Dr. Mills to discuss urologists perspective on use of ProstaScint scan**
6/13/96	Comments on agenda for meeting with FDA on June 18, 1996
6/13/96	Conversation with Mr. Madoo about participants for Advisory Committee and guidance on presentation.
6/14/96	Revised agenda for meeting on June 18, 1996
6/14/96	Intent to file amendment to PLA re: letter of June 11, 1996 from FDA
6/15/96	Fax to Dr. Mills/Dr. Epps of table of performance characteristics for 5 highest accruing sites from 356In15
6/17/96	Additional information requested by Dr. Mills; bone scan and image information

6/20/96	Conversation with Dr. Epps re proposed telephone conference to discuss errors in FDA 6/11/96 letter; confirmation of datasets with Gleason sum information had been previously sent to Dr. Misra
6/20/96	**List of attendees for MIDAC meeting**
6/24/96	Confirmation of telephone conference to be set for 6/28/96.
6/25/96	Details of inaccuracies in 6/11/96 not-approvable letter
6/26/96	Copies of overheads from 6/18/96 meeting; additional information to provide to FDA
6/27/96	Confirmation of phone conference for 6/28; request for copies of overheads presented at 6/18 meeting;Gleason sum information for Dr. Misra
7/1/96	**Discussion of Risk Analysis presented at 6/18/96 meeting**
7/3/96	**Request from Dr. Misra for disc of clinical information**
7/3/96	Proposed indication statement; details of logistic regression analyses and SPSS outputs
7/3/96	Copies of slides and analysis output to support the logistic regression risk analysis as requested by FDA
7/9/96	Listing of patients with extra fossa disease detected by ProstaScint and confirmed by other tests
7/10/96	Information requested by Dr. Mills on biopsy patients in 356In16
7/10/96	Discussion of logistics of Advisory meeting
7/10/96	**Request for listing of patients for 356In16 who did not have biopsy;information on "indeterminate" patients**
7/11/96	Further discussion of logistics of Advisory meeting
7/11/96	Information on three additional patients
7/11/96	Copy of room dimensions for Advisory Committee meeting
7/11/96	40 copies of MIDAC briefing document; 21 copies of Image book sent to FDA for MIDAC committee
7/12/96	**Briefing document for MIDAC members and consultants**

7/15/96		Comments on FDAs revised Advisory Committee briefing document
7/17/96		**Request for dosimetry estimate/f/u information on 12 patients from 356In15**
7/18/96		**Copy of questions for MIDAC committee**
7/18/96		**F/U on dosimetry question and f/u on 12 indeterminate patients from 356In15**
7/18/96		Suggested questions from Tom McKearn
7/18/96		Radiation dosimetry and 356In15 patient follow up as requested by Dr. Mills
7/18/96		Information on subsets of patients
7/24/96		Response to request for radiation dosimetry from Dr. Randy Brill
7/26/96		Confirmation that CYTO needs to respond to the not-approvable letter, but can use the Advisory Committee's comments as appropriate; clarification requested on current CBER position re promotional materials
7/30/96		Request to update labeling for Indiclor (Amersham)
7/30/96		Letter to Epps informing of request to manufacturers of Indium to resubmit necessary labeling
8/1/96		Copies of package insert on hardcopy and disc
8/1/96		Response to the not approvable letter of 6/11/95
8/8/96		Information on commercial lots to be used for launch; stability tables for consistency lots; current lot release protocols for bulk and final container release
8/13/96	Phone	Conversation re PI; offer to meet w/ FDA after first review to expedite
8/15/96	Phone	Indication of intent to request to meet w/ FDA to review and resolve issues from the PI.
8/16/96		Letter from T. McKearn to J. Seigel suggesting face to face meeting to finalise PI
8/16/96		Request for face to face meeting after J. Siegel review completed

8/19/96		Additional discs of PI in DOS version
8/21/96	**Phone**	**Discussion of request for face to face meeting to negotiate PI information.**
8/23/96	Phone	Update on progress of PI revisions
8/30/96		**Faxed copy of FDA PI recommendations**
9/9/96	**Phone**	**Request for identification of location in PLA of indium supplier information; query as to when revised PI will be submitted**
9/18/96		Revised version of prescribing information
9/19/96	**Fax**	**Revised labeling information**
9/25/96	Phone	Labeling issues
9/26/96	Fax	Proofs of labeling changes requested by FDA
9/27/96	Phone	Discussion of Indium suppliers
9/30/96	Phone	Meeting set for review of labeling on 10/11/96
10/1/96	**Phone**	**Further discussion of indium suppliers in PLA**
10/3/96	Phone	Further discussion of indium suppliers and PI version
10/4/96	**Fax**	**Revised labeling information attached to FDA 2567**
10/7/96	**Phone**	**Verification of reciept of PI from FDA; discussion of changes made**
10/3/96		**Revised labeling changes comments - form 2567**
10/9/96		Agenda for 10/11/96 meeting to review prescribing information
10/14/96		Revised PI changes based on 10/11/96 meeting
10/15/96		Sample cases of imaging performance with Mallinckrodt indium
10/21/96	Fax	Proposed revision to labeling to clarify sections FDA had questions on
10/22/96	Fax	Clarification of case from study 356In19 of bone lesion in femoral neck
10/23/96	**Fax**	**P.I. and request to provide maximum dosage for ProstaScint**

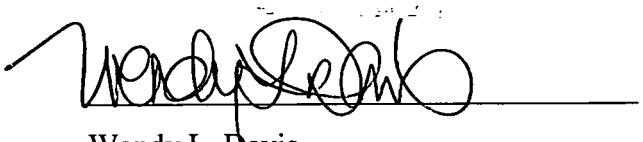
10/24/96	Fax	Modification of paragraph under Imaging performance in PI
10/24/96	**Phone**	**Additional request for information: color copies of final vial labels and kit box; overdosage section of PI; maximum dose; question on planned promotional campaign; request for press release**
10/24/96	**Phone**	**Confirmation of receipt of changes to PI**
10/24/96	**Phone**	**Discussion of remaining issues re: FDA's latest version of PI**
10/24/96	Fax	Latest version of PI
10/25/96	Phone	Discussion on press release with Bill Purves
10/25/96		Submission of label proofs and Overdosage section of PI
10/25/96	**Phone**	**Discussion of statement in proposed PI about ITLC radiochemical purity test**
10/28/96	Fax	Changes to PI requested by FDA
10/28/96	Phone	Status on signoff of approval letter; request for final version of PI without highlighted changes; discussion of press release
10/28/96	Fax	PI minus highlights and strikeouts
10/28/96	**Phone**	**Request for change in PI statement (changes faxed through)**
10/28/96		**APPROVAL LETTER FOR PROSTASCINT**
10/30/96	**Phone**	**Comments on draft press release**
11/1/96	Phone	Questions to FDA re: request for copies of approved labeling (**FDA said ok to send out**) and notification of magenta-colored cap being put on product rather than aqua-colored (**FDA said ok to use until aqua-capped becomes available**)
11/4/96	Phone	Question on expiry of 4-year period for sodium acetate solution; question on requirement for the General Safety Test. FDA will respond to both of these
11/6/96	**Phone**	**4-year expiry period for sodium acetate solution accepted by FDA; General Safety Test can be dropped from release testing specifications**

11/18/96	Phone	RSNA booth panels for review
11/19/96		Labeling/promotional items for review; poster panels for display at RSNA; PI - Galley proof; publications
11/21/96	**Phone**	**Discussion of RSNA panels, handout of RSNA panel, banner, publication reprints, package insert with Bill Purvis**
11/21/96	Phone	Call to Bill Purvis to discuss comments on PIE panel for RSNA meeting and review of information
12/3/96	Phone	Query on what documentation needed to submit to inform of change in deionized water system
12/17/96		New Drug Listing
12/18/96		Form FDA 2567, kit box, labels for vials, prescribing information
12/19/96		Form 2567; letter mailed to study sites participating in study 356In21
1/7/97	Phone	Notification of launch materials to be submitted
1/8/97		Introductory adverstising and promotional materials to be used in launch
1/13/97	Phone	Follow up on launch materials submitted for review
1/15/97	Phone	Request for information from Carol Brodnick, reviewer for ProstaScint labeling and promotional pieces; request for 10/29/96 press release; PI for files; comment on type font
1/20/97	Phone	Discussion of proposed introductory advertising and promotional material for launch.
1/21/97	Phone	Discussion of launch pieces with FDA
1/21/97	**Fax**	**Fair Balance Statements**
1/22/97	Fax	Revised flow diagram for recurrent disease patients
1/22/97	**Fax**	**Memo listing agreement on advertising and promotional materials**
1/23/97	**Fax**	**Comments on revised flow diagram**
1/30/97		Distribution report 12/1/96-12/31/96
1/31/97		Submission of sales aid piece, copy of PI

2/3/97	**Fax**	**Revised flow chart**
2/4/97		Technical Users Guide promotional information
2/4/97		PIE promotional information (includes PI)
2/10/97		Periodic AE report 10/29/96-1/30/97
2/13/97	Fax	Revised promotional piece "Code B" from submssion of 1/8/97
2/17/97		Contents of Internet Homepage with regards to presentation of information re: ProstaScint
2/17/97		Notification of reprints that were not submitted at RSNA meeting in November 1996.
2/24/97		PIE introduction brochure
2/24/97		Nuc. Med. Brochure
2/24/97		PIE Introduction package
2/25/97		Medwatch form - AE report
3/4/97		Form 2567 - Post-it Note Pad - Alternating ProstaScint/OncoScint

In view of the above, applicant asserts that the Application is now in compliance with 37 CFR 1.740(a)(11).

Respectfully submitted,
CYTOGEN Corporation



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